In the Specification

Please substitute the following paragraph on page 1, beginning at line 6:

[0001] This application is a continuation-in-part of PCT application PCT/IB01/01891, filed July 26, 2001, which claims priority to U.S. provisional application No. 60/223,482, now abandoned, filed August 7, 2000, both of which are herein incorporated by reference in their entireties.

Please substitute the following paragraph on page 5, beginning at line 20 through to page 6, line 4:

[00013] The approximately 150kb genomic region associated with schizophrenia was found to contain the candidate gene g34872. In addition to characterizing the intron-exon structure of the g34872 gene, a range of mRNA splicing variants including tissue specific mRNA splicing variants were identified, and the existence of the mRNA was demonstrated. Subsequently, a peptide fragment derived from the g34872 polypeptide product, the amino acid sequence of which is shown in SEQ ID ~~No~~ NO: 5, caused a decrease in locomotor movement frequency, and an increase in stereotypy when injected intraperitoneally in mice. Further discussion of the identification of the g34872 gene is provided in copending U.S. patent application ser. no. 09/539,333 titled "Schizophrenia associated genes, proteins and biallelic markers" and copending International Patent Application No. PCT/IB00/00435, both filed 30 March 2000 and incorporated herein by reference in their entireties.

Please substitute the following paragraphs on page 10, beginning at line 1:

[00024] SEQ ID ~~No~~ NO: 1 contains a cDNA sequence of PAPAP.

[00025] SEQ ID ~~No~~ NO: 2 contains the amino acid sequence encoded by the cDNA of SEQ ID ~~No~~ NO: 1.

[00026] SEQ ID ~~No~~ NO: 3 contains a genomic DNA sequence of PAPAP.

[00027] SEQ ID ~~No~~ NO: 4 contains a DNA sequence encoding a g34872 peptide-alkaline phosphatase fusion protein described in example 1.

[00028] SEQ ID ~~No~~ NO: 5 contains a DNA sequence encoding a g34872 peptide used to

identify and clone the PAPAP gene, as described in example 1.

[00029] SEQ ID ~~No~~ NO: 6 contains the amino acid sequence encoded by the DNA of SEQ ID ~~No.~~ NO: 4.

Please substitute the following paragraph on page 21, beginning at line 4:

[0061] Variants of polynucleotides according to the invention include, without being limited to, nucleotide sequences which are at least 95% identical to a polynucleotide of SEQ ID ~~Nos~~ NOs: 1 or 3 or to any polynucleotide fragment of at least 12 consecutive nucleotides of a polynucleotide of SEQ ID ~~Nos~~ NOs: 1 or 3, and preferably at least 99% identical, more particularly at least 99.5% identical, and most preferably at least 99.8% identical to a polynucleotide of SEQ ID ~~Nos~~ NOs: 1 or 3 or to any polynucleotide fragment of at least 12 consecutive nucleotides of a polynucleotide of SEQ ID ~~No~~ NOs: 1 or 3.

Please substitute the following paragraphs on page 26, beginning at line 17 through to page 27, line 22:

[0079] The present invention concerns the genomic sequence of PAPAP. The present invention encompasses the PAPAP gene, or PAPAP genomic sequences consisting of, consisting essentially of, or comprising the sequence of SEQ ID ~~No~~ NO: 3, a sequence complementary thereto, as well as fragments and variants thereof. These polynucleotides may be purified, isolated, or recombinant.

[0080] PAPAP nucleic acids include isolated, purified, or recombinant polynucleotides comprising, consisting essentially of, or consisting of a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides of SEQ ID ~~No~~ NO: 3 or the complements thereof. PAPAP nucleic acids may also include isolated, purified, or recombinant polynucleotides comprising, consisting essentially of, or consisting of a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides selected from the group of nucleotide positions 1 to 3038, 1 to 421, 422 to 557, 2158 to 2218 and 2620 to 3039 of SEQ ID ~~No~~ NO: 3, or the complements thereof. The invention also encompasses a purified, isolated, or recombinant polynucleotide comprising a nucleotide sequence having at least 70, 75, 80,

85, 90, or 95% nucleotide identity with a nucleotide sequence of SEQ ID ~~No~~ NO: 3 or a complementary sequence thereto or a fragment thereof. The nucleotide differences as regards to the nucleotide sequence of SEQ ID ~~No~~ NO: 3 may be generally randomly distributed throughout the entire nucleic acid. Nevertheless, preferred nucleic acids are those wherein the nucleotide differences as regards to the nucleotide sequence of SEQ ID ~~No~~ NO: 3 are predominantly located outside the coding sequences contained in the exons. These nucleic acids, as well as their fragments and variants, may be used as oligonucleotide primers or probes in order to detect the presence of a copy of the PAPAP gene in a test sample, or alternatively in order to amplify a target nucleotide sequence within the PAPAP sequences. Another object of the invention consists of a purified, isolated, or recombinant nucleic acid that hybridizes with the nucleotide sequence of SEQ ID ~~No~~ NO: 3 or a complementary sequence thereto or a variant thereof, under stringent hybridization conditions as defined above.

Please substitute the following paragraphs on page 28, beginning at line 2 through to page 29, line 12:

[0082] The expression of the PAPAP gene has been shown to lead to the production of at least one mRNA species, the nucleic acid sequence of which is set forth in SEQ ID ~~No~~ NO: 1.

[0083] Another object of the invention is a purified, isolated, or recombinant nucleic acid comprising the nucleotide sequence of SEQ ID ~~No~~ NO: 1, complementary sequences thereto, as well as allelic variants, and fragments thereof. Moreover, preferred polynucleotides of the invention include purified, isolated, or recombinant PAPAP cDNAs consisting of, consisting essentially of, or comprising the sequence of SEQ ID ~~No~~ NO: 1. Particularly preferred nucleic acids of the invention include isolated, purified, or recombinant polynucleotides comprising, consisting essentially of, or consisting of a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides of SEQ ID ~~No~~ NO: 1 or the complements thereof. Nucleic acids of the invention also include isolated, purified, or recombinant polynucleotides comprising a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides of SEQ ID ~~No~~ NO: 1 or the complements thereof, wherein said contiguous span comprises at least 1, 2, 3, 5, or 10 of the following nucleotide positions of SEQ ID ~~No~~ NO: 1: 1 to

140, 141 to 460, 460 to 690, 87 to 346 and 691 to 1104. Additional preferred embodiments of the invention include isolated, purified, or recombinant polynucleotides comprising a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides of SEQ ID ~~No~~ NO: 1 or the complements thereof, wherein said contiguous span comprises a biallelic marker.

[0084] The invention also pertains to a purified or isolated nucleic acid comprising a polynucleotide having at least 95% nucleotide identity with a polynucleotide of SEQ ID ~~No~~ NO: 1, advantageously 99 % nucleotide identity, preferably 99.5% nucleotide identity and most preferably 99.8% nucleotide identity with a polynucleotide of SEQ ID ~~No~~ NO: 1, or a sequence complementary thereto or a biologically active fragment thereof.

[0085] Another object of the invention relates to purified, isolated or recombinant nucleic acids comprising a polynucleotide that hybridizes, under the stringent hybridization conditions defined herein, with a polynucleotide of SEQ ID ~~No~~ NO: 1, or a sequence complementary thereto or a variant thereof or a biologically active fragment thereof.

[0086] The cDNA of SEQ ID ~~No~~ NO: 1 includes a 5'-UTR region starting from the nucleotide at position 1 and ending at the nucleotide in position 86 of SEQ ID ~~No~~ NO: 1. The cDNA of SEQ ID ~~No~~ NO: 1 includes a 3'-UTR region starting from the nucleotide at position 347 and ending at the nucleotide at position 1104 of SEQ ID ~~No~~ NO: 1. The polyadenylation signal starts from the nucleotide at position 1085 and ends at the nucleotide in position 1104 of SEQ ID ~~No~~ NO: 1.

Please substitute the following paragraph on pate 30, beginning at line 2:

[0089] The PAPAP open reading frame is contained in the corresponding mRNA of SEQ ID ~~No~~ NO: 1. More precisely, the effective PAPAP coding sequence (CDS) includes the region between nucleotide position 87 (first nucleotide of the ATG codon) and nucleotide position 346 (end nucleotide of the TGA codon) of SEQ ID ~~No~~ NO: 1. The present invention also embodies isolated, purified, and recombinant polynucleotides which encode a polypeptides comprising a contiguous span of at least 6 amino acids, preferably at least 8 or 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2.

Please substitute the following paragraph on page 30, beginning at line 21:

[0092] Polynucleotides derived from the 5' and 3' regulatory regions are useful in order to detect the presence of at least a copy of a nucleotide sequence of SEQ ID ~~No~~ NO: 3 or a fragment thereof in a test sample.

Please substitute the following paragraph on page 30, beginning at line 21:

[0094] In order to identify the relevant biologically active polynucleotide fragments or variants of SEQ ID ~~No~~ NO: 3, one of skill in the art will refer to the book of Sambrook *et al.*(Sambrook, 1989) which describes the use of a recombinant vector carrying a marker gene (i.e. beta galactosidase, chloramphenicol acetyl transferase, etc.) the expression of which will be detected when placed under the control of a biologically active polynucleotide fragments or variants of SEQ ID ~~No~~ NO: 3. Genomic sequences located upstream of the first exon of the PAPAP gene are cloned into a suitable promoter reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβgal-Basic, pβgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech, or pGL2-basic or pGL3-basic promoterless luciferase reporter gene vector from Promega. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, luciferase, β galactosidase, or green fluorescent protein. The sequences upstream the PAPAP coding region are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for increasing transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the inserted upstream sequence.

Please substitute the following paragraph on page 33, beginning at line 1:

[0098] Thus, the present invention also concerns a purified or isolated nucleic acid comprising a polynucleotide which is selected from the group consisting of the 5' and 3' regulatory regions, or a sequence complementary thereto or a biologically active fragment or variant thereof. In one aspect, the "5' regulatory region" comprises the nucleotide sequence located between positions 1 and 421 of SEQ ID ~~No~~ NO: 3. In one aspect, the "3' regulatory region" comprises the nucleotide sequence located between positions 3040 and 3189 of SEQ ID ~~No~~ NO: 3.

Please substitute the following paragraph on page 34, beginning at line 1:

[0103] "Biologically active" polynucleotide derivatives of SEQ ID ~~No~~ NO: 3 are polynucleotides comprising or alternatively consisting in a fragment of said polynucleotide which is functional as a regulatory region for expressing a recombinant polypeptide or a recombinant polynucleotide in a recombinant cell host. It could act either as an enhancer or as a repressor.

Please substitute the following paragraph on page 34, beginning at line 12:

[0105] The regulatory polynucleotides of the invention may be prepared from the nucleotide sequence of SEQ ID ~~No~~ NO: 3 by cleavage using suitable restriction enzymes, as described for example in Sambrook *et al.* (1989). The regulatory polynucleotides may also be prepared by digestion of SEQ ID ~~No~~ NO: 3 by an exonuclease enzyme, such as Bal31 (Wabiko *et al.*, 1986). These regulatory polynucleotides can also be prepared by nucleic acid chemical synthesis, as described elsewhere in the specification.

Please substitute the following paragraph on page 36, beginning at line 13:

[0114] The desired polypeptide encoded by the above-described nucleic acid may be of various nature or origin, encompassing proteins of prokaryotic or eukaryotic origin. Among the polypeptides expressed under the control of a PAPAP regulatory region include bacterial, fungal or viral antigens. Also encompassed are eukaryotic proteins such as intracellular proteins, like "house keeping" proteins, membrane-bound proteins, like receptors, and secreted proteins like endogenous mediators such as cytokines. The desired polypeptide may be the PAPAP protein, especially the protein of the amino acid sequence of SEQ ID ~~No~~ NO: 2, or a fragment or a variant thereof.

Please substitute the following paragraph on page 37, beginning at line 13:

[0118] The desired polypeptide encoded by the above-described nucleic acid may be of various nature or origin, encompassing proteins of prokaryotic or eukaryotic origin. Among the polypeptides expressed under the control of a PAPAP regulatory region include bacterial, fungal or viral antigens. Also encompassed are eukaryotic proteins such as intracellular proteins, like "house keeping" proteins, membrane-bound proteins, like receptors, and secreted proteins like endogenous mediators such as cytokines. The desired polypeptide may be the PAPAP protein, especially the protein of the amino acid sequence of SEQ ID ~~No~~ NO: 2, or a fragment or a variant thereof.

Please substitute the following paragraph on page 42, beginning at line 23 through to page 43, line 5:

[0134] Other compositions containing a vector of the invention comprising an oligonucleotide fragment of the nucleic sequence SEQ ID ~~No~~ NO: cDNA, preferably a fragment including the start codon of the PAPAP gene, as an antisense tool that inhibits the expression of the corresponding PAPAP gene. Preferred methods using antisense polynucleotide according to the present invention are the procedures described by Sczakiel *et al.*(1995) or those described in PCT Application No WO 95/24223, the disclosures of which are incorporated by reference herein in their entirety.

Please substitute the following paragraphs on page 43, beginning at line 23, through to page 45, line 25:

[0138] Polynucleotides derived from the PAPAP gene are useful in order to detect the presence of at least a copy of a nucleotide sequence of SEQ ID ~~No~~ NO: 1 or 3, or a fragment, complement, or variant thereof in a test sample. Such methods are useful, e.g., in the diagnosis of disorders resulting from or associated with an alteration in PAPAP gene expression, as well as to confirm PAPAP gene expression in cells or samples in which PAPAP expression has been induced, e.g., for experimental or therapeutic purposes.

[0139] Particularly preferred probes and primers of the invention include isolated, purified, or

recombinant polynucleotides comprising a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides of SEQ ID ~~No~~ NO: 3 or the complements thereof. Probes and primers also include isolated, purified, or recombinant polynucleotides comprising a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides of SEQ ID ~~No~~ NO: 3 or the complements thereof, wherein said contiguous span comprises at least one of the following nucleotide positions of SEQ ID ~~No~~ NO: 3: 1 to 3038, 1 to 421, 422 to 557, 2158 to 2218 and 2620 to 3039. Additional preferred probes and primers of the invention include isolated, purified, or recombinant polynucleotides comprising a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides of SEQ ID ~~No~~ NO: 1 or the complements thereof. Further preferred probes and primers of the invention include isolated, purified, or recombinant polynucleotides comprising a contiguous span of at least 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 500, or 1000 nucleotides of SEQ ID ~~No~~ NO: 1 or the complements thereof, wherein said contiguous span comprises at least one of the following nucleotide positions of SEQ ID ~~No~~ NOs: 1: 1 to 140, 141 to 460, 460 to 690, 87 to 346 and 691 to 1104.

[0140] Thus, the invention also relates to nucleic acid probes characterized in that they hybridize specifically, under the stringent hybridization conditions defined above, with a nucleic acid selected from the group consisting of the nucleotide sequences of SEQ ID ~~Nos~~ NOs: 1 and 3, or a variant thereof or a sequence complementary thereto.

[0141] In one embodiment the invention encompasses isolated, purified, and recombinant polynucleotides consisting of, or consisting essentially of a contiguous span of 8 to 50 nucleotides of any one of SEQ ID ~~Nos~~ NOs: 1, 3 and the complement thereof, wherein said span includes a PAPAP-related biallelic marker in said sequence or a biallelic marker in linkage disequilibium with PAPAP; optionally, wherein said contiguous span is 18 to 35 nucleotides in length and said biallelic marker is within 4 nucleotides of the center of said polynucleotide; optionally, wherein said polynucleotide consists of said contiguous span and said contiguous span is 25 nucleotides in length and said biallelic marker is at the center of said polynucleotide; optionally, wherein the 3' end of said contiguous span is present at the 3' end of said polynucleotide; and optionally, wherein the 3' end of said contiguous span is located at the 3' end of said polynucleotide and said biallelic marker is present at the 3' end of said

polynucleotide.

[0142] In another embodiment the invention encompasses isolated, purified and recombinant polynucleotides comprising, consisting of, or consisting essentially of a contiguous span of 8 to 50 nucleotides of SEQ ID ~~Nos~~ NOs: 1, 3, or the complements thereof, wherein the 3' end of said contiguous span is located at the 3' end of said polynucleotide, and wherein the 3' end of said polynucleotide is located within 20 nucleotides upstream of a PAPAP-related biallelic marker in said sequence or a biallelic marker in linkage disequilibrium therewith.

[0143] In an additional embodiment, the invention encompasses polynucleotides for use in hybridization assays, sequencing assays, and enzyme-based mismatch detection assays for determining the identity of the nucleotide at a PAPAP-related biallelic marker in SEQ ID ~~Nos~~ NOs: 1, 3, or the complements thereof, as well as polynucleotides for use in amplifying segments of nucleotides comprising a PAPAP-related biallelic marker in SEQ ID ~~Nos~~ NOs: 1, 3, or the complements thereof.

Please substitute the following paragraphs on page 49, beginning at line 24, through to page 50, line 15:

[0153] Consequently, the invention also comprises a method for detecting the presence of a nucleic acid comprising a nucleotide of SEQ ID ~~Nos~~ NOs: 1 or 3, a fragment or a variant thereof and a complementary sequence thereto in a sample, said method comprising the following steps of:

a) bringing into contact a nucleic acid probe or a plurality of nucleic acid probes which can hybridize with a nucleotide sequence included in a nucleic acid of SEQ ID ~~Nos~~ NOs: 1 or 3, a fragment or a variant thereof and a complementary sequence thereto and the sample to be assayed; and

b) detecting the hybrid complex formed between the probe and a nucleic acid in the sample.

[0154] The invention further concerns a kit for detecting the presence of a nucleic acid comprising a nucleotide sequence of SEQ ID ~~Nos~~ NOs: 1 or 3, a fragment or a variant thereof and a complementary sequence thereto in a sample, said kit comprising:

a) a nucleic acid probe or a plurality of nucleic acid probes which can hybridize with a

nucleotide sequence included in a nucleic acid of SEQ ID ~~Nos~~ NOs: 1 or 3, a fragment or a variant thereof and a complementary sequence thereto; and

b) optionally, the reagents necessary for performing the hybridization reaction.

Please substitute the following paragraph on page 53, beginning at line 9:

[0161] The term "PAPAP polypeptides" is used herein to embrace all of the proteins and polypeptides of the present invention. Also forming part of the invention are polypeptides encoded by the polynucleotides of the invention, as well as fusion polypeptides comprising such polypeptides. The invention embodies PAPAP proteins from humans, including isolated or purified PAPAP proteins consisting of, consisting essentially of, or comprising the sequence of SEQ ID ~~No~~ NO: 2.

Please substitute the following paragraphs on page 53, beginning at line 15 through to page 55, line 5:

[0163] The invention concerns the polypeptide encoded by a nucleotide sequence of SEQ ID ~~No~~ NO: 1 or 3, or a complementary sequence thereto or a fragment thereof.

[0164] The present invention embodies isolated, purified, and recombinant polypeptides comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2. In other preferred embodiments the contiguous stretch of amino acids comprises the site of a mutation or functional mutation, including a deletion, addition, swap or truncation of the amino acids in the PAPAP protein sequence.

[0165] The invention also encompasses purified, isolated, or recombinant polypeptides comprising an amino acid sequence having at least 70, 75, 80, 85, 90, 95, 98 or 99% amino acid identity with the amino acid sequence of SEQ ID ~~No~~ NO: 2 or a fragment thereof. The variant polypeptides are included in the present invention regardless of whether they have their normal biological activity. This is because even where a particular polypeptide molecule does not have biological activity, one of skill in the art would still know how to use the polypeptide, for instance, as a vaccine or to generate antibodies. Other uses of the polypeptides of the present invention that do not have PAPAP activity include, inter alia, as epitope tags, in epitope mapping, and as molecular

weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods known to those of skill in the art. As described below, the polypeptides of the present invention can also be used to raise polyclonal and monoclonal antibodies, which are useful in assays for detecting PAPAP protein expression or as agonists and antagonists capable of enhancing or inhibiting PAPAP protein function. Further, such polypeptides can be used in the yeast two-hybrid system to "capture" PAPAP protein binding proteins, which are also candidate agonists and antagonists according to the present invention.

[0166] In other embodiments, the present invention also concerns complexes formed by PAPAP and g34872 polypeptides. Thus the invention comprises a purified, isolated, or recombinantly produced complex of at least one PAPAP polypeptide and at least one g34872 polypeptide, wherein said PAPAP polypeptide comprises at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2. In a preferred embodiment, said g34872 polypeptide comprises at least 6 amino acids, preferably at least 8 to 10 amino acids of SEQ ID ~~No~~ NO: 5. Analogous complexes between PAPAP and CaM-II kinases are also encompassed by the present invention.

Please substitute the following paragraph on page 57, beginning at line 3:

[0172] Any PAPAP cDNA, including SEQ ID ~~No~~ NO: 1, can be used to express PAPAP proteins and polypeptides. The nucleic acid encoding the PAPAP protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The PAPAP insert in the expression vector may comprise the full coding sequence for the PAPAP protein or a portion thereof. For example, the PAPAP derived insert may encode a polypeptide comprising at least 10 consecutive amino acids of the PAPAP protein of SEQ ID ~~No~~ NO: 2.

Please substitute the following paragraph beginning on page 57, line 19 through to page 58, line 13:

[0174] In one embodiment, the entire coding sequence of the PAPAP cDNA through the poly A signal of the cDNA is operably linked to a promoter in the expression vector. Alternatively, if the

nucleic acid encoding a portion of the PAPAP protein lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the insert from the PAPAP cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using BglI and SalI restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The nucleic acid encoding the PAPAP protein or a portion thereof is obtained by PCR from a bacterial vector containing the PAPAP cDNA of SEQ ID ~~No~~ NO: 2 using oligonucleotide primers complementary to the PAPAP cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5' primer and BglII at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the sequence encoding the PAPAP protein or a portion thereof is positioned properly with respect to the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with PstI, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with BglII.

Please substitute the following paragraphs on page 60, beginning at line 16 through to page 61, line 10:

[0184] One antibody composition of the invention is capable of specifically binding, or specifically binds, to the PAPAP protein of SEQ ID ~~No~~ NO: 2. For an antibody composition to specifically bind to PAPAP, it must demonstrate at least a 5%, 10%, 15%, 20%, 25%, 50%, or 100% greater binding affinity for a full length first variant of the PAPAP protein than for a full length second variant of the PAPAP protein in an ELISA, RIA, or other antibody-based binding assay.

[0185] In a preferred embodiment, the invention concerns antibody compositions, either polyclonal or monoclonal, that selectively binds to an epitope-containing a polypeptide comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2.

[0186] In other embodiments, the present invention comprises antibody compositions, either polyclonal or monoclonal, that selectively binds to a complex of PAPAP and g34872 polypeptides, wherein said PAPAP polypeptide comprises at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2. In a preferred embodiment, said g34872 polypeptide comprises at least 6 amino acids, preferably at least 8 to 10 amino acids of SEQ ID ~~No~~ NO: 5. In another embodiment, the present invention provides antibody compositions that selectively binds to a complex of PAPAP and CaM-KII.

Please substitute the following paragraphs on page 64, beginning at line 3:

[0194] Consequently, the invention is also directed to a method of binding an anti-PAPAP antibody to a PAPAP polypeptide, or of detecting specifically the presence of a PAPAP polypeptide according to the invention in a biological sample, said method comprising the following steps:

a) bringing into contact the biological sample with a polyclonal or monoclonal antibody that specifically binds a PAPAP polypeptide comprising an amino acid sequence of SEQ ID ~~No~~ NO: 2, or to a peptide fragment or variant thereof; and

b) detecting the antigen-antibody complex formed.

[0195] The invention also concerns a diagnostic kit for detecting *in vitro* the presence of a PAPAP polypeptide according to the present invention in a biological sample, wherein said kit comprises:

a) a polyclonal or monoclonal antibody that specifically binds a PAPAP polypeptide comprising an amino acid sequence of SEQ ID ~~No~~ NO: 2, or to a peptide fragment or variant thereof, optionally labeled;

b) a reagent allowing the detection of the antigen-antibody complexes formed, said reagent carrying optionally a label, or being able to be recognized itself by a labeled reagent, more particularly in the case when the above-mentioned monoclonal or polyclonal antibody is not labeled by itself.

Please substitute the following paragraph on page 72, beginning at line 22 through to page 73, line 2:

[0215] In a first preferred embodiment, a recombinant vector of the invention is used to amplify the inserted polynucleotide derived from a PAPAP genomic sequence of SEQ ID ~~No~~ NO: 3 or a PAPAP cDNA, for example the cDNA of SEQ ID ~~No~~ NO: 1 in a suitable cell host, this polynucleotide being amplified at every time that the recombinant vector replicates.

Please substitute the following paragraph on page 73, beginning at line 16:

[0217] More particularly, the present invention relates to expression vectors which include nucleic acids encoding a PAPAP protein, preferably the PAPAP protein of the amino acid sequence of SEQ ID ~~No~~ NO: 2 or variants or fragments thereof.

Please substitute the following paragraph on page 74, beginning at line 3:

[0219] The invention also pertains to a recombinant expression vector useful for the expression of the PAPAP coding sequence, wherein said vector comprises a nucleic acid of SEQ ID ~~No~~ NO: 1.

Please substitute the following paragraphs on page 75, beginning at line 19 through to page 76, line 3:

[0223] The *in vivo* expression of a PAPAP polypeptide of SEQ ID ~~No~~ NO: 2 or fragments or variants thereof may be useful in order to correct a genetic defect related to the expression of the native gene in a host organism or to the production of a biologically inactive PAPAP protein.

[0224] Consequently, the present invention also comprises recombinant expression vectors mainly designed for the *in vivo* production of the PAPAP polypeptide of SEQ ID ~~No~~ NO: 2 or fragments or variants thereof by the introduction of the appropriate genetic material in the organism of the patient to be treated. This genetic material may be introduced *in vitro* in a cell that has been previously extracted from the organism, the modified cell being subsequently reintroduced in the said organism, directly *in vivo* into the appropriate tissue.

Please substitute the following paragraphs on page 79, beginning at line 20 through to page 80, line 3:

[0239] A suitable vector for the expression of the PAPAP polypeptide of SEQ ID ~~No~~ NO: 2 or fragments or variants thereof is a baculovirus vector that can be propagated in insect cells and in insect cell lines. A specific suitable host vector system is the pVL1392/1393 baculovirus transfer vector (Pharmingen) that is used to transfect the SF9 cell line (ATCC No. CRL 1711) which is derived from *Spodoptera frugiperda.*

[0240] Other suitable vectors for the expression of the PAPAP polypeptide of SEQ ID ~~No~~ NO: 2 or fragments or variants thereof in a baculovirus expression system include those described by Chai *et al.* (1993), Vlasak *et al.* (1983) and Lenhard *et al.* (1996).

Please substitute the following paragraph on page 84, beginning at line 10:

[0257] Another object of the invention comprises a host cell that has been transformed or transfected with one of the polynucleotides described herein, and in particular a polynucleotide either comprising a PAPAP regulatory polynucleotide or the coding sequence of the PAPAP polypeptide of SEQ ID ~~Nos~~ NOs: 1 or 3, or a fragment or a variant thereof. Also included are host cells that are transformed (prokaryotic cells) or that are transfected (eukaryotic cells) with a recombinant vector such as one of those described above. More particularly, the cell hosts of the present invention can comprise any of the polynucleotides described in the "Genomic Sequences Of ~~t~~The The PAPAP Gene" section, the "PAPAP cDNA Sequences" section, the "Coding Regions" section, the "Polynucleotide constructs" section, and the "Oligonucleotide Probes And Primers" section.

Please substitute the following paragraph on page 96, beginning at line 23:

[0297] In preferred embodiments of the cell and non-cell based assays, said PAPAP peptide comprising a contiguous span of at least 4, 6 or 8 contiguous amino acids of SEQ ID ~~Nos.~~ NO: 2.

Please substitute the following paragraph on page 98, beginning at line 1:

[0302] In another aspect, an animal based assay of the invention encompasses a method for identifying a compound for the treatment of schizophrenia or bipolar disorder comprising (a) exposing an animal to a level of PAPAP activity sufficient to cause a schizophrenia-related or bipolar disorder-related symptom or endpoint, and (b) exposing said animal to a test compound. A

test compound can then be selected according to its ability to ameliorate said schizophrenia-related or bipolar disorder-related endpoints. PAPAP activity may be provided by any suitable method, including but not limited to providing a vector containing a PAPAP nucleotide sequence, treating said animal with a compound capable of increasing PAPAP expression and treating said cell with a PAPAP peptide. Preferably, said animal is treated with a PAPAP peptide comprising a contiguous span of at least 4, 6 or preferably 8 ~~contigous~~ contiguous amino acids of SEQ ID ~~Nos.~~ NOs: 2. Preferably the test compound is a compound capable of or suspected to be capable of ameliorating a symptom of schizophrenia, bipolar disorder or a related disorder; alternatively, the test compound is suspected of exacerbating a symptom of schizophrenia, bipolar disorder or a related disorder. A test compound capable of ameliorating any detectable symptom or endpoint of a schizophrenia, bipolar disorder or a related disorder may be selected for use in developing medicaments.

Please substitute the following paragraphs on page 101, beginning at line 5:

[0309] As an illustrative example, to study the interaction of the PAPAP protein, or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2, with drugs or small molecules, such as molecules generated through combinatorial chemistry approaches, the microdialysis coupled to HPLC method described by Wang *et al.* (1997) or the affinity capillary electrophoresis method described by Bush *et al.* (1997), the disclosures of which are incorporated by reference, can be used.

[0311] In further methods, peptides, drugs, fatty acids, lipoproteins, or small molecules which interact with the PAPAP protein, or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2, may be identified using assays such as the following. The molecule to be tested for binding is labeled with a detectable label, such as a fluorescent, radioactive, or enzymatic tag and placed in contact with immobilized PAPAP protein, or a fragment thereof under conditions which permit specific binding to occur. After removal of non-specifically bound molecules, bound molecules are detected using appropriate means.

Please substitute the following paragraphs on page 102, beginning at line 6 through to page 103, line 16:

[0314] A method for the screening of a candidate substance comprises the following steps:

a) providing a polypeptide comprising, consisting essentially of, or consisting of a PAPAP protein or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2;

b) obtaining a candidate substance;

c) bringing into contact said polypeptide with said candidate substance;

d) detecting the complexes formed between said polypeptide and said candidate substance.

[0315] In one embodiment, the invention relates to the use of PAPAP for the study of g34872 pathway in CNS disorders. Methods for screening for interacting substances may be used to detect interaction of PAPAP and g34872. Thus, the invention also comprises:

a) providing a polypeptide comprising, consisting essentially of, or consisting of a PAPAP protein or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2;

b) obtaining a g34872 polypeptide;

c) bringing into contact said PAPAP polypeptide with a g34872 polypeptide;

d) detecting the complexes formed between said PAPAP polypeptide and said g34872 polypeptide.

[0316] Preferably, said g34872 polypeptide comprises at least 4, 6 or preferably 8 contiguous amino acids of the amino acid sequence of SEQ ID ~~No~~ NO: 5.

[0317] The invention further concerns a kit for the screening of a candidate substance interacting with the PAPAP polypeptide, wherein said kit comprises:

a) a PAPAP protein having an amino acid sequence selected from the group consisting of the amino acid sequences of SEQ ID ~~No~~ NO: 2 or a peptide fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more

preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2;

b) optionally means useful to detect the complex formed between the PAPAP protein or a peptide fragment or a variant thereof and the candidate substance.

Please substitute the following paragraph on page 105, beginning at page 10:

[0323] Alternatively, peptides, drugs or small molecules which bind to the PAPAP protein, or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2, may be identified in competition experiments. In such assays, the PAPAP protein, or a fragment thereof, is immobilized to a surface, such as a plastic plate. Increasing amounts of the peptides, drugs or small molecules are placed in contact with the immobilized PAPAP protein, or a fragment thereof, in the presence of a detectable labeled known PAPAP protein ligand. For example, the PAPAP ligand may be detectably labeled with a fluorescent, radioactive, or enzymatic tag. The ability of the test molecule to bind the PAPAP protein, or a fragment thereof, is determined by measuring the amount of detectably labeled known ligand bound in the presence of the test molecule. A decrease in the amount of known ligand bound to the PAPAP protein, or a fragment thereof, when the test molecule is present indicated that the test molecule is able to bind to the PAPAP protein, or a fragment thereof.

Please substitute the following paragraph on page 106, beginning at line 1:

[0324] Proteins or other molecules interacting with the PAPAP protein, or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2, can also be found using affinity columns which contain the PAPAP protein, or a fragment thereof. The PAPAP protein, or a fragment thereof, may be attached to the column using conventional techniques including chemical coupling to a suitable column matrix such as agarose, ~~Affi-Gel®~~ AFFI-GEL, or other matrices familiar to those of skill in art. In some embodiments of this method, the affinity column contains chimeric proteins in which the PAPAP protein, or a fragment thereof, is fused to glutathion S transferase (GST). A mixture of cellular proteins or pool of expressed proteins as described above is applied to the affinity column. Proteins or other molecules interacting with the

PAPAP protein, or a fragment thereof, attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen *et al.* (1997), the disclosure of which is incorporated by reference. Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

Please substitute the following paragraph on page 106, beginning at line 19 through to page 107, line 14:

[0325] Proteins interacting with the PAPAP protein, or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2, can also be screened by using an Optical Biosensor as described in Edwards and Leatherbarrow (1997) and also in Szabo *et al.* (1995), the disclosures of which are incorporated by reference. This technique permits the detection of interactions between molecules in real time, without the need of labeled molecules. This technique is based on the surface plasmon resonance (SPR) phenomenon. Briefly, the candidate ligand molecule to be tested is attached to a surface (such as a carboxymethyl dextran matrix). A light beam is directed towards the side of the surface that does not contain the sample to be tested and is reflected by said surface. The SPR phenomenon causes a decrease in the intensity of the reflected light with a specific association of angle and wavelength. The binding of candidate ligand molecules cause a change in the refraction index on the surface, which change is detected as a change in the SPR signal. For screening of candidate ligand molecules or substances that are able to interact with the PAPAP protein, or a fragment thereof, the PAPAP protein, or a fragment thereof, is immobilized onto a surface. This surface comprises one side of a cell through which flows the candidate molecule to be assayed. The binding of the candidate molecule on the PAPAP protein, or a fragment thereof, is detected as a change of the SPR signal. The candidate molecules tested may be proteins, peptides, carbohydrates, lipids, or small molecules generated by combinatorial chemistry. This technique may also be performed by immobilizing eukaryotic or prokaryotic cells or lipid vesicles exhibiting an endogenous or a recombinantly expressed PAPAP protein at their surface.

Please substitute the following paragraph on page 108, beginning at line 4:

[0329] The bait protein or polypeptide comprises, consists essentially of, or consists of a PAPAP polypeptide or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID ~~No~~ NO: 2.

Please substitute the following paragraph on page 113, beginning at line 15:

[0348] In a further embodiment, the nucleic acid comprising the nucleotide sequence of the 5' regulatory region or a biologically active fragment or variant thereof also includes a 5'UTR region of the PAPAP cDNA of SEQ ID ~~No~~ NO: 1, or one of its biologically active fragments or variants thereof.

Please substitute the following paragraphs on page 114, beginning at line 4 through to page 115, line 9:

[0351] In another embodiment of a method for the screening of a candidate substance or molecule that modulates the expression of the PAPAP gene, wherein said method comprises the following steps:

a) providing a recombinant host cell containing a nucleic acid, wherein said nucleic acid comprises a 5'UTR sequence of the PAPAP cDNA of SEQ ID ~~No~~ NO: 1, or one of its biologically active fragments or variants, the 5'UTR sequence or its biologically active fragment or variant being operably linked to a polynucleotide encoding a detectable protein;

b) obtaining a candidate substance; and

c) determining the ability of the candidate substance to modulate the expression levels of the polynucleotide encoding the detectable protein.

[0352] In a specific embodiment of the above screening method, the nucleic acid that comprises a nucleotide sequence selected from the group consisting of the 5'UTR sequence of the PAPAP cDNA of SEQ ID ~~No~~ NO: 1 or one of its biologically active fragments or variants, includes a promoter sequence which is endogenous with respect to the PAPAP 5'UTR sequence.

[0353] In another specific embodiment of the above screening method, the nucleic acid that comprises a nucleotide sequence selected from the group consisting of the 5'UTR sequence of the PAPAP cDNA of SEQ ID ~~No~~ NO: 1 or one of its biologically active fragments or variants, includes a promoter sequence which is exogenous with respect to the PAPAP 5'UTR sequence defined therein.

[0354] In a further preferred embodiment, the nucleic acid comprising the 5'-UTR sequence of the PAPAP cDNA or SEQ ID ~~No~~ NO: 1 or the biologically active fragments thereof includes a PAPAP-related biallelic marker, or the complements thereof.

[0355] The invention further comprises with a kit for the screening of a candidate substance modulating the expression of the PAPAP gene, wherein said kit comprises a recombinant vector that comprises a nucleic acid including a 5'UTR sequence of the PAPAP cDNA of SEQ ID ~~No~~ NO: 1, or one of their biologically active fragments or variants, the 5'UTR sequence or its biologically active fragment or variant being operably linked to a polynucleotide encoding a detectable protein.

Please substitute the following paragraphs on page 128, beginning at line 1:

[0402] In preferred embodiments, medicaments of the invention act on PAPAP, either by acting directly on PAPAP, a subunit associated with a PAPAP complex, a PAPAP-g34872 complex, a PAPAP-CaM-KII complex, or indirectly, by acting on the PAPAP pathway. For example, the medicaments may modulate, and more preferably decrease the level of PAPAP activity which occurs in a cell or particular tissue, or increase or ~~descrease~~ decrease the activity of the PAPAP protein. In certain embodiments, the invention thus comprises use of a compound capable of increasing or decreasing PAPAP expression or PAPAP protein activity in the preparation or manufacture of a medicament. Preferably, said compound is used for the treatment of a psychiatric disease, preferably for the treatment of schizophrenia or bipolar disorder. Preferably, said compound acts directly by binding to PAPAP, g34872, CaM-KII, or a PAPAP receptor. Said g34872 may be any g34872 polypeptide, including the polypeptide of SEQ ID ~~No~~ NO: 5 or a polypeptide described in copending patent application no. 09/539,333 titled "Schizophrenia associated genes, proteins and biallelic markers", filed 30 March 2000. Said Cam-KII can be any calcium-calmodulin kinase II, preferably CaM-kII alpha or CaM-KII beta.

[0403] Such medicaments may also increase or decrease the activity of a compound analogous to PAPAP, a compound comprising an amino acid sequence having at least 25% amino acid identity to the sequence of SEQ ID ~~No~~ NO: 2, a compound comprising an amino acid sequence having at least 50% amino acid identity to the sequence of SEQ ID ~~No~~ NO: 2, and a compound comprising an amino acid sequence having at least 80% amino acid identity to the sequence of SEQ ID ~~No~~ NO: 2.

Please substitute the following paragraph on page 130, beginning at line 19 through to page 131, line 12:

[0408] In another aspect, one or more PAPAP biallelic markers, polymorphisms or variants can also be used to develop diagnostics tests capable of identifying individuals who express a detectable trait as the result of a specific genotype or individuals whose genotype places them at risk of developing a detectable trait at a subsequent time. The trait analyzed using the present diagnostics may be used to diagnose any detectable trait, including predisposition to schizophrenia or bipolar disorder or a related disorder such as those described in the examples above, age of onset of detectable symptoms, a beneficial response to or side effects related to treatment against one of said disorders. Such a diagnosis can be useful in the monitoring, prognosis and/or prophylactic or curative therapy of the disorder. These diagnostic techniques are based on the knowledge of the PAPAP nucleic acid sequence and may employ a variety of methodologies to determine whether a test subject has a genotype associated with an increased risk of developing a detectable trait or whether the individual suffers from a detectable trait as a result of a particular mutation, including methods which enable the analysis of individual chromosomes for haplotyping, such as family studies, single sperm DNA analysis or somatic hybrids. These diagnostic techniques can involve the detection of specific alleles present within the PAPAP sequence, including in PAPAP regulatory sequences or generally in the human chromosome 13q33 region. More particularly, the invention concerns the detection of a nucleic acid comprising at least one of the nucleotide sequences of SEQ ID ~~Nos.~~ NOs: 1 or 3, or a fragment thereof or a complementary sequence thereto.

Please substitute the following paragraph on page 139, beginning at line 17:

[0431] An in-frame fusion of a cDNA sequence encoding the PAP peptide amino acid sequence (SEQ ID ~~No~~ NO: 5) with the C-terminus of secreted alkaline phosphatase (AP) was created in a pAPtag expression vector. The nucleotide and amino acid sequence of the (fusion) protein sequence inserted in the vector are shown in SEQ ID ~~Nos~~ NOs: 4 and 6 respectively.